CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-571/S-008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW OF A SUPPLEMENTAL NEW DRUG APPLICATION

NDA 20,571/SE7-008 **Submission Date:** April 17, 1998

Drug Name:	Camptosar® (Irinotecan HCl)
Formulation:	Injectable
Sponsor:	Pharmacia & Upjohn Company Kalamazoo, MI 49001
Reviewer:	Lydia V. Kieffer, Pharm.D.
Type of Submission:	Supplement from accelerated approval to full approval status for the current second-line indication.

SYNOPSIS

Irinotecan is a topoisomerase I inhibitor and a derivative of camptothecin. Pharmacia & Upjohn Company have submitted this supplemental NDA to support a transition from the present accelerated approval status to full approval status for the current indication for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-fluorouracil (5-FU)-based therapy. An additional dose is being proposed for the same indication. The current dose consist of a starting dose of 125 mg/m^2 weekly for 4 weeks followed by 2 weeks of rest. An additional dose is being proposed in which patients will receive 350 mg/m^2 once every 3 weeks.

In support of the new dosing regimen, the sponsor has submitted 3 pharmacokinetic studies: one study has been conducted in the U.S. and is in a phase I setting, the other two pharmacokinetic studies were conducted in Europe (one is a phase I and the other a phase II study) and were submitted as supportive studies to the U.S. study. The two European studies have been published in a peer-reviewed journal and the articles were submitted.

U.S. Phase I Study (P&U Study M/6475/0024) - Miller 1998

A single-center, open-label, uncontrolled, dose-escalation phase I trial was conducted in order to identify the MTD of irinotecan administered at a starting dose of 240 mg/m^2 infused over 90 minutes once every three weeks in patients with solid tumors for which no standard therapy was available. Subsequent dose levels for additional patient accrual included 290, 320, 340, 390, 450, 520, 600, 690, and 760 mg/m^2. CPT-11 was supplied by Pharmacia & Upjohn. Tumor types included colorectal (N=32), esophagus (N=1), and gall bladder (N=1). The pharmacokinetic objective of this study was to obtain a pharmacokinetic profile of CPT-11 and its metabolites, SN-38 and SN-38-glucuronide (SN-38G), at the doses and schedule previously

mentioned. Plasma samples were collected from 34 patients (21 males/13 females) on week 1 of their first cycle. However, patients were allowed to continue therapy until tumor progression, unacceptable toxicity, serious intercurrent illness, or withdrawal at the patient's request. Time points of blood sampling were pre-infusion, 45 and 90 minutes after the start of the infusion, then at 5, 10, 15, 30 minutes, and at 1, 2, 4, 6, 8, 10, 12, 24, 32, and 48 hours post infusion. Plasma sampling was collected out to 4 t½s for CPT-11, 2 t½s for SN-38, and almost 3 t½s for SN-38G. Plasma samples were assayed for CPT-11 and SN-38 through methods previously described SN-38G was estimated as the increase in SN-38 concentration following incubation of plasma with β-glucuronidase (see Assay methods section). Pharmacokinetic parameters were calculated through non-compartmental methods. The MTD was identified to be 320 mg/m^2 for patients who had not received prior abdominal and/or pelvic radiotherapy (AP-RT) and 290 mg/m^2 for patients with prior APRT. Six patients received 340 mg/m^2, of which 3 were ≥ 65 years of age. One of the six patients (a 46 year old previously treated man) was able to tolerate more than 1 cycle at the 340 mg/m^2 dose level (received 3 cycles). The rest of the patients received 1 cycle. DLTs were diarrhea and neutropenia for no prior AP-RT and diarrhea, neutropenia, and vomiting for patients with prior AP-RT. CPT-11 concentrations predominated in human plasma with a C_{max} observed usually at the end of the 90-minute infusion and a mean elimination half-life of 12 hours. SN-38 and SN-38G C_{max} levels were about 60-fold and 20-fold lower than the corresponding CPT-11 levels, respectively. Mean CPT-11 CL and Vd values (13.0 ± 3.8 L/h/m^2 and 227 ± 85.9 L/ m^2) across all dose levels were comparable to previously reported values. A summary of all pharmacokinetic parameters for all dose levels can be found in Table A-3 of the appendix. Large interpatient variability in CPT-11, SN-38, and SN-38G $AUC_{0-\infty}$ values were observed possibly due to small patient numbers at each dose level making a dose proportionality assessment not possible. The mean metabolic ratio (percent SN-38 $AUC_{0-\infty}$ /CPT-11 $AUC_{0-\infty}$) was 3.3% of the parent $AUC_{0-\infty}$. No differences of statistical significance in CPT-11 dose-normalized C_{max}, dose-normalized $AUC_{0-\infty}$, CL, Vd, or t½ were observed across the dose range of mg/m^2 when an analysis of variance was performed. A relationship between CPT-11, SN-38, or SN-38G $AUC_{0-\infty}$ values and CPT-11 dose were not observed possibly due to sampling. The sponsor believes that the lack of observed correlation between $AUC_{0-\infty}$ and dose is likely related to interpatient variability, the small numbers of patients examined at each dose level, and the narrow dose range over which $AUC_{0-\infty}$ values were determined. One colorectal cancer patient died suddenly while on study after receiving their third cycle of therapy. Grade 1 and 2 adverse events were reported during the first 2 courses of therapy. During cycle one the patient experienced grade 2 dyspnea lasting 8 days which resulted in a dose reduction to 240 mg/m^2 for the subsequent second and third cycle. The principal investigator considered the death to be treatment related; however the study director attributed the death to atherosclerotic coronary artery disease due to the patients smoking history, hypertension, diabetes mellitus, and peripheral vascular disease. No toxicokinetics were reported on this patient. Study results have been included in the appendix for additional information.

European Phase I Study (Study CPT-101) – Abigerges 1995

A phase I and pharmacologic study was conducted in 64 patients (24 women/40 men) with solid tumors refractory to standard therapy in order to determine the MTD of CPT-11 administered as a 30-minute IV infusion every 3 weeks and describe any toxicities of the drug. The pharmacokinetic objective of the study was to describe CPT-11 and SN-38 from a pharmacokinetic perspective and observe any pharmacokinetic/ pharmacodynamic relationships the drug may have. Primary sites of involvement included colon, head and neck, lung, and pleura. CPT-11 was supplied by

The starting dose was 100 mg/m^2 every 3 weeks with subsequent escalation levels of 150, 200, 230, 260, 300, 350, 400, 450, 500, 600, and 750 mg/m^2 with no intrapatient dose escalation permitted. Blood sampling was performed at time 0, then at 10, 20, and 30 minutes during the 30-minute infusion followed by additional collection at 5, 10, 15, 30, 45 and 60 minutes, and at 2, 4, 8, 12, 24, and 36 hours postinfusion. Blood sampling was collected to 96 hours in 20 cases in order to better determine the terminal t½ of both CPT-11 and SN-38. Urine sampling was also collected at 6-hour fractions. CPT-11 and SN-38 levels were determined by methods described in the assay section of this review. Pharmacokinetic information for analysis was obtained from 60 patients (94 courses) of which 7 were at the 350 mg/m^2 dose level. The recommended dose from this phase I trial due to safety reasons is 350 mg/m^2 every 3 weeks even though the observed MTD was 600 mg/m^2 IV over 30 minutes every 3 weeks with dose-limiting granulocytopenia. At the recommended dose, the use of high-dose loperamide was required due to significant diarrhea in order to dose escalate any further. Mean CPT-11 C_{max} levels ranged from 2.3 to 13 μg/mL with either a biphasic or triphasic decay profile that demonstrated a terminal phase t½ of 14.2 ± 0.9 hours in both cases. The mean Vd was 157 ± 8 L/m^2 and was stable as a function of dose, CL (mean 15 L/h/ m^2) did not vary with increases in doses either, demonstrating linearity. Interpatient variability was observed in CPT-11 total AUC; but a direct relationship was noted between CPT-11 doses and corresponding CPT-11 total AUCs ($r = 0.86$, $P < 0.001$). Mean SN-38 C_{max} levels ranged from 32 to 299 ng/mL with a T_{max} of 1.1 hours from the start of the infusion. Mean apparent terminal t½ of SN-38 was 13.8 ± 1.4 hours mirroring that of CPT-11. SN-38 AUC was directly related to the CPT-11 dose ($r = 0.60$, $P < 0.001$) and correlated significantly to corresponding CPT-11 AUC ($r = 0.60$, $P < 0.001$, data not included in article), possibly demonstrating linearity. Urinary excretion of CPT-11 and SN-38 accounted for 19.9 ± 1.4% and 0.25 ± 0.03% of the CPT-11 dose, respectively. Saliva samples were collected from 2 patients receiving the 450 mg/m^2 dose level at the end of the infusion representing 105 and 28% of the corresponding plasma concentration. One patient at the same dose level had sweat samples analyzed which represented 11% of the corresponding plasma sample at the end of the infusion. Two patients underwent pleural fluid sampling collection representing 7 and 19% of the corresponding plasma level at the end of the infusion at the dose level of 300 mg/m^2. Rebound plasma concentrations of CPT-11 and SN-38 were observed at about 0.5 to 1 hour post infusion, possibly indicative of enterohepatic recycling. A significant percent decrease in WBCs and granulocytes was observed with increase of CPT-11 and SN-38

AUCs. A direct correlation between CPT-11 and SN-38 AUC increases with diarrhea, nausea, and vomiting was noted. One patient died on day 8 of study who presented in renal failure and encephalopathy with status epilepticus after receiving the 400 mg/m^2 dose level; however no toxicokinetic data was available in the article and an autopsy was not performed. The full literature report can be found in the appendix.

Abigerges D, Chabot GG, Armand JP, Herait P, Gouyette A, Gandia D. Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients. *J Clin Oncol 1995; 13: 210-21.*

Phase II Study (Study CPT-205) – Canal 1996[1]

A pharmacokinetic and pharmacodynamic study was performed during a phase II trial in 213 advanced colorectal cancer patients (26 men/21 women for pharmacokinetic assessment) previously treated with adjuvant and/or one regimen of palliative 5-FU based therapy. The pharmacokinetic objectives of this trial was to estimate the pharmacokinetic parameters, define interpatient and intrapatient pharmacokinetic variations and to investigate pharmacokinetic/pharmacodynamic relationships with respect toxicity and clinical outcome of CPT-11 and its metabolites. The 47 patients involved in the pharmacokinetic assessment portion of the phase II study represented the study population well in terms of age, sex, performance status, primary tumor site, metastatic sites, and previous chemotherapeutic treatment history. Thirty-three out of the 47 patients had pharmacokinetic assessment for SN-38G. Cpt-11 was supplied by The phase II dose was 350 mg/m^2 IV over 30 minutes once every three weeks. A limited sampling strategy developed by Chabot[2] was adopted for this trial in which three CPT-11 plasma sample collection times (time 0, then 0.5, 1, and 6 hours postinfusion) was used to estimate CPT-11 and SN-38 pharmacokinetics. CPT-11 and SN-38 extraction was performed by HPLC methods described in the assay section of this review. Mean CPT-11 total CL was 15.2 ± 4.3 L/h•m^2. Mean relative metabolic ratio of total SN-38 AUC to CPT-11 AUC ($(AUC_{SN-38} + AUC_{SN-38G})/AUC_{CPT-11}$) was 0.17 ± 0.09. Extensive glucuronidation of SN-38 to SN-38G was evidenced by a 6.5-fold higher AUC for SN-38G than for SN-38. Interindividual variation in CPT-11, SN-38, and SN-38G AUCs was 30%, 89.5%, and 70.4%, respectively. Interestingly, interindividual variation in the metabolic ratio was 51.6%. Twenty-three patients received more than one cycle of chemotherapy and were part of the intraindividual pharmacokinetic analysis which revealed a coefficient of variation in CPT-11 CL of 13.5%. The CVs in AUC for SN-38 and SN-38G were 35.1% and 37.9%, respectively. The corresponding intraindividual metabolic ratio was 32.6%. Pharmacokinetic analysis was performed during the first cycle in 40 out of the 47 patients enrolled and cycle number did not seem to influence any of the pharmacokinetic parameters of CPT-11, SN-38, or metabolic ratios. A relationship between the percent reduction in neutrophil count and CPT-11 and SN-38 AUC ($r = 0.597$, $P < 0.001$ and $r = 0.559$, $P < 0.001$, respectively) was observed when an analysis of hematologic toxicity was performed during the first cycle of therapy. A minor relationship between the intensity of delayed diarrhea and CPT-11 AUC was observed ($P = 0.042$). No relationship was observed between tumor response and CPT-11, SN-38, and SN-38G pharmacokinetic parameters.

1. Canal P, Gay C, Dezeuze A, Douillard JY, Bugat R, Brunet R, Adenis A, Herait P, Lokiec F, Mathieu-Boue A. Pharmacokinetics and pharmacodynamics of irinotecan during a phase II clinical trial in colorectal cancer. *J Clin Oncol 1996; 14(10): 2688-95.*
2. Chabot GG: Development of limited sampling models for the simultaneous estimation of irinotecan (CPT-11) and active metabolite SN-38 pharmacokinetics. Cancer Chemother Pharmacol 1995; 36: 463-472.

Assay Methods:

Studies CPT-101 and CPT-205:
These two literature reports utilized an assay previously described in the original NDA submission located in Volume 1.38, page 6/3/81.

COMMENTS:

General

1) In study 0024 the MTD was identified to be 320 mg/m^2 for patients who had not received prior abdominal and/or pelvic radiotherapy (AP-RT) and 290 mg/m^2 for patients with prior APRT. Six patients received 340 mg/m^2, of which 3 were ≥ 65 years of age. One of the six patients (a 46 year old previously treated man) was able to tolerate more than 1 cycle at the 340 mg/m^2 dose level (received 3 cycles). The rest of the patients received 1 cycle. DLTs were diarrhea and neutropenia for no prior AP-RT and diarrhea, neutropenia, and vomiting for patients with prior AP-RT.

   Large interpatient variability in CPT-11, SN-38, and SN-38G $AUC_{0-\infty}$ values were observed possibly due to small patient numbers at each dose level making a dose proportionality assessment not possible. No differences of statistical significance in CPT-11 dose-normalized C_{max}, dose-normalized $AUC_{0-\infty}$, CL, Vd, or t½ were observed across the dose range of mg/m^2 when an analysis of variance was performed. A relationship between CPT-11, SN-38, or SN-38G $AUC_{0-\infty}$ values

and CPT-11 dose were not observed possibly due to sampling. The Agency concurs that the lack of observed correlation between $AUC_{0-\infty}$ and dose may be related to interpatient variability, the small numbers of patients examined at each dose level, and the narrow dose range over which $AUC_{0-\infty}$ values were determined.

Reasons that may explain why the MTD in this trial was 320 mg/m^2 for patients with no prior APRT and 290 mg/m^2 for patients with prior APRT may lie in the smaller number of patients, worse baseline performance status, and overall older patients that were enrolled in comparison to the European trial.

Even though the US trial (0024) was unable to achieve the MTD that the two European trials achieved, the CL of CPT-11 across the 3 submitted pharmacokinetic studies indicate consistency in the pharmacokinetic results as evidenced by table A-7 in the appendix (mean of 13.9 ± 4 L/h/m^2 for US study 0024, 11 ± 2 L/h/m^2 for study 101, and 15.2 ± 4.3 L/h/m^2 for study 205). The t½ in study 0024 and 101 were reported as similar (11.7 ± 1, and 11.2 ± 1.3, respectively) as well.

2) The Agency will be awaiting the submission of the non-IND pediatric studies results mentioned in Volume 17.1, page 2/1/5 for review and possible consideration for inclusion in the labeling at that time.

3) We remind the sponsor that our original agreement to complete and submit results from 4 Clinical Pharmacology and Biopharmaceutics studies outlined in our letter dated June 14th, 1996 specifically on pages 3 and 4 is an essential element to approval.

Labeling

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

RECOMMENDATION:

1) We remind the sponsor to adequately address the Clinical Pharmacology and Biopharmaceutics commitments stated in the Agency's original letter dated June 14th, 1996.

2) Please forward the above general comments to the sponsor.

3) Please forward the above labeling comments to the sponsor.

4) The sponsor should make the necessary changes to the proposed package insert according to the labeling comments provided in the comments section of the review.

/S/ 10-9-98

Lydia V. Kieffer, Pharm.D.
Reviewer
Division of Pharmaceutical Evaluation I

/S/ 10/9/98

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

cc: Orig 20,571
HFD-150/ Division File
HFD-150/ PGuinn, GWilliams, IChico
HFD-850/ LLesko
HFD-860/ HMalinowski, MMehta, ARahman, LKieffer
HFD-340/Vishwanathan
CDR BMurphy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-571/S-008

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-571/S-008

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

APR 27 1998

Attention: John S. Walker
Regulatory Affairs Manager

Dear: Mr Walker,

We acknowledge receipt of your supplemental application for the following:

Name of Drug: CAMPTOSAR Injection

NDA Number: 20-571

Supplement Number: S-008

Date of Supplement: April 17,1998

Date of Receipt: April 22,1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 21, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug
Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Sincerely,

/S/

for Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-571/S-008
HFD-150/Div. Files
HFD-150/CSO/PGuinn 4/24/98

filename:

SUPPLEMENT ACKNOWLEDGEMENT

ITEM 13 & 14
PATENT INFORMATION AND CERTIFICATION

1. Active Ingredient	Irinotecan hydrochloride
2. Strengths	20 mg/mL (100 mg/5 mL and 40 mg/2 mL)
3. Tradename	CAMPTOSAR® Injection
4. Dosage Form Route of Administration	Injection Intravenous
5. Applicant Firm Name	Pharmacia & Upjohn
6. NDA Number	20-571
7. Approval Date	June 14, 1996 (original NDA)
8. Patent Information	Irinotecan hydrochloride is claimed *per se* in United States Patent 4,604,463, which expires August 15, 2007
9. Patent Certification	Pharmacia & Upjohn hereby certifies that irinotecan hydrochloride is claimed *per se* in United States Patent 4,604,463 which expires August 15, 2007

EXCLUSIVITY SUMMARY for NDA # sNDA 20-571 **SUPPL #** S-008

Trade Name Camptosar Injection **Generic Name** irinotecan hydrochloride injection

Applicant Name Pharmacia & Upjohn **HFD-** 150

Approval Date, if known _____

PART I **IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /___/ NO /X/

   b) Is it an effectiveness supplement?

   YES /X/ NO /___/

   If yes, what type? (SE1, SE2, etc.) SE7

   Full Approval Status from Accelerated Approval Status.

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

Form OGD-011347 Revised 8/27/97

cc: Original NDA 20-571 Division File HFD 150 HFD-93 Mary Ann Holovac

HFD 150/PGuinn

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /X/ NO /___/ OTC Switch /___/

If yes, NDA # 20-571 Drug Name Camptosar (irinotecan hydrochloride injection) Injection
Full Approval Status from Accelerated Approval Status.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

Signature
Title: _____

10/17/98
Date

/S/

Signature of Division Director

10/19/98
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

DEBARMENT CERTIFICATION FOR NDA 20-571

Camptosar (NDA 20-571) full approval supplemental NDA

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Edward L. Patt

2/13/98

Ed L. Patt
Manager
Regulatory Compliance

Date

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # sNDA 20-571 Supplement # S-008 Circle one: SE1 SE2 SE3 SE4 SE5 SE6 (SE7)

HFD-150 Trade (generic) name/dosage form: Camptosar Injection (Irinotecan hydrochloride injection) Action: (AP) AE NA

Applicant Pharmacia & Upjohn Therapeutic Class Cytotoxic (5010100)

Indication(s) previously approved Accelerated Approval for treatment of patients with metastatic carcinoma of the colon or rectum whose disease progressed following 5-FU-based therapy Pediatric labeling of approved indication(s) is adequate ___ inadequate ___ N/A

Indication in this application Full Approval for treatment of patients with metastatic carcinoma of the colon or rectum whose disease progressed following 5-FU-based therapy (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

X 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.
~~No Pediatric Studies have been done.~~ No Data from Pediatric studies have been submitted.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/

Signature of Preparer and Title (PM, CSO, MO, other) 10/2/01 Date

cc: Orig NDA/PLA # 20-571
HFD-150 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-571/S-008

CORRESPONDENCE

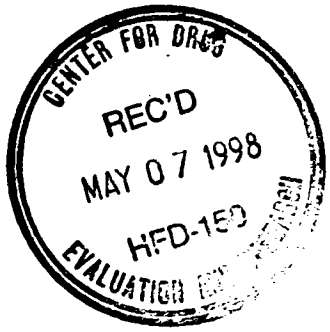
Pharmacia & Upjohn

Office of:
John S. Walker
Regulatory Affairs Manager

Mailstop: 0636-298-113
Telephone: 616/833-8263
Fax: 616/833-8273

April 17, 1998

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852



Re: NDA 20-571
CAMPTOSAR® Injection
(Irinotecan Hydrochloride Injection)

NDA Supplement
Full Approval Supplement

Dear Sir or Madam:

Under the provisions of 21 CFR 314.71, we are submitting the enclosed 141 volume supplement to NDA 20-571. The supplemental NDA (sNDA) seeks a transition from the current accelerated approval status to full approval status. This supplement consists of the following components:

Cover Letter
- Attachment 1 - Form 356h
- Attachment 2 - User Fee Cover Sheet
- Attachment 3 - Certification of CMC Field Copy
- Attachment 4 - Debarment Statement
- Attachment 5 - Pagination System

Item 11: Location of Case Report Tabulations (Volume 1)

Case Report Tabulations (CRTs) for studies V301, V302 and 0024 are provided as data listings in the appendices of the respective study reports. The locations of these report sections are provided in Item 11.

Items 13 & 14: Patent Certification/Exclusivity (Volume 1)

Item 1: Overall Table of Contents (Volume 1)

Item 2: Annotated proposed package insert (Volume 1)

Item 3: Application Summary (Volume 1)

Item 4: Chemistry, Manufacturing and Control Section (Volume 2)

This section includes information in support of the higher Infusion Solution concentration that results from the additional dosage schedule being proposed.

Item 6. Human Pharmacokinetics Section (Volume 6-11)

This section includes information on the pharmacokinetics of CPT-11 and SN-38 associated with the additional dosage schedule being proposed.

Item 8/10. Clinical/Statistical Sections (Item 8: Volume 12-72;
Item 10: Volume 73-134)

Two phase III, adequate and well-controlled studies) are the primary component of this sNDA. These studies were conducted by and provide direct evidence of the clinical benefits of CPT-11. In study CPT-11 was compared to no active treatment, except best supportive care; and in study CPT-11 was compared to infusional 5-FU.

Item 12: Case Report Forms for patients who either died or discontinued treatment due to adverse events (Volume 134-141)

We are providing an archival copy of all volumes listed above and review copies for Items 2, 3, 4, 6, and 8/10. Attachment 5 in Volume 1 provides an explanation of the pagination system used in this sNDA.

As agreed during the pre-NDA meeting of December 11, 1997, one desk copy of SAS datasets and associated documentation for studies is also being provided in this submission.

In conjunction with this sNDA, we have submitted a User Fee to the in the amount of However, based on discussions at the pre-NDA meeting and on conversations in January, 1998 between myself and Mike Jones, CSO, FDA Office of Center Director, we understand that a User Fee may not actually be required for this sNDA. We therefore request your assistance in determining whether a user fee is required and that a refund be made, if appropriate.

If you have questions related to this submission, please contact me at (616) 833-8263 or address correspondence to mailstop 0636-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

John S. Walker
Regulatory Affairs Manager

JSW:law

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Pharmacia & Upjohn Company

DATE OF SUBMISSION
April 17, 1998

TELEPHONE NO. *(Include Area Code)*
616-833-8263

FACSIMILE (FAX) Number *(Include Area Code)*
616-833-8273

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
7000 Portage Road
Kalamazoo, Michigan 49001

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Irinotecan hydrochloride injection

PROPRIETARY NAME *(trade name)* IF ANY
CAMPTOSAR® Injection

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*
CPT-11 U-101440E

DOSAGE FORM:
Injection

STRENGTHS:
20 mg/mL

ROUTE OF ADMINISTRATION:
Intravenous

(PROPOSED) INDICATION(S) FOR USE:
Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☒ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 141

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND Nos: DMF Nos:

This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
John S. Walker	John S. Walker Regulatory Affairs Manager	April 17, 1998

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
7000 Portage Road Kalamazoo, Michigan 49001	(616)833-8263

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

FORM FDA 356h (7/97)